John von Neumann Institute for Computing

Dewetting in Nanoscale Hydrophobic Plates Collapse and Protein Complex Folding

Ruhong Zhou

published in

NIC Workshop 2006,
From Computational Biophysics to Systems Biology,
Jan Meinke, Olav Zimmermann,
Sandipan Mohanty, Ulrich H.E. Hansmann (Editors)
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. **34**, ISBN-10: 3-9810843-0-6,
ISBN-13: 978-3-9810843-0-6, pp. 53-58, 2006.

http://www.fz-juelich.de/nic-series/volume34

Dewetting in Nanoscale Hydrophobic Plates Collapse and Protein Complex Folding

Ruhong Zhou[1,2]

[1] IBM Thomas J. Watson Research Center,
Yorktown Heights, NY 10598
E-mail: ruhongz@us.ibm.com

[2] Department of Chemistry,
Columbia University, New York, NY 10027

We have performed molecular dynamics simulations of the collapse of graphite-like model plates, fluorinated carbon monolayers, and protein melittin tetramer, to examine how water molecules mediate hydrophobic collapse in nanoscale (size 3-4nm) hydrophobic plates as well as protein complexes (with similar sizes). We found that the normal graphite plates do not display any dewetting (water drying) transition during the double plate collapse, while a reduction in carbon-water van der Waals interaction will result in a dewetting transition, consistent with previous findings from carbon nanotubes. On the other hand, the fluorinated carbon plates display a strong dewetting transition with a critical distance up to 10Å and a very fast collapse speed ($\sim$100ps). In the melittin tetramer folding, we also observed an unexpected dewetting transition inside a nanoscale channel formed by the tetramer, with a channel size of up to 2-3 water diameters. These dewetting transitions, although occurring on a microscopic length scale, are reminiscent of the first order phase transition from liquid to vapor, which provide an enormous driving force towards the further collapse.

1 Introduction

Hydrophobic effects play a key role in many important physio-chemical processes, such as protein folding, micelle formation, water permeation in membrane channels (aquaporins), capillary evaporation, and superhydrophobic surface coating. Many biomolecules are characterized by surfaces containing extended nonpolar regions, and the aggregation and subsequent removal of water molecules between these hydrophobic surfaces is believed to be crucial. It is now widely known that small hydrophobic solutes hydrate differently than large ones. Small solutes such as methane can fit into the water hydrogen bond network without destroying much of the hydrogen bonds[1], whereas larger hydrophobic solutes induce reorganization of water molecules.[2–4] More interestingly, there might exist a drying layer as large as several water molecules around strongly hydrophobic surfaces, as first suggested by Stillinger[5] and then studied by many other groups[6–8] (interested readers can refer to the review by Pratt[8] for more details). Most of these early studies focus on single plates (solutes) using macroscopic theories or simplified computational models. One recent study on double plates also adopted such a simplified model where the solute-water interaction is purely repulsive.[9] Water dramatically reorganizes between such plates as they are brought together, so much so, that for inter-plate distances smaller than a certain critical distance D_c, there is a spontaneous drying transition, which is reminiscent to the first order liquid-vapor phase transition.[9] When the solute-water interaction enhances, the dewetting transition is expected to be weaker and weaker until completely disappears.[9] In this mini-review, we go over some of our recent studies on the dewetting transition in more

realistic systems, from all-atom graphite-like plates, to fluorinated carbon monolayers, and protein complexes. Some interesting and striking results have been found.

2 Results and Discussion

2.1 Graphite-like Plates

We first use graphite-like plates to study how sensitive the dewetting transition is to the solute-solvent attractions and how water contact angle can be a useful guide in estimating the dewetting critical distance. Figure 1 shows the diagram of the double graphite-plate system, with each graphite plate consisting of 170 carbon atoms and a diameter of $\sim$28Å. The graphite plates are then solvated in a $60 \times 60 \times 60$ Å^3 SPC water box. A series of 1.0 ns NPT molecular dynamics (MD) simulations are then performed after the standard equilibration (see Method section for details). It is found that the graphite plates with normal interaction (ϵ_{CC}=0.086 kcal/mol and ϵ_{CO}= 0.1156 kcal/mol) do not show any dewetting transition no matter how close we push the double plates (of course no water molecule can stay in-between the plates once the separation is so small, $\leq$6.2Å, that the steric effect takes control). This is consistent with previous studies with carbon nanotubes and graphite plates.[10,11] More simulations are then followed with the reduced water-carbon interactions to study the drying transition sensitivity. The inter-plate distance is fixed at 6.8Å but the strength of the water-plate interaction is decreased gradually. When the water-carbon interaction ϵ_{CO} is decreased to 0.0611 kcal/mol (ϵ_{CC}=0.024kcal/mol), the dewetting transition is observed.[12] When the water-carbon interaction is further reduced, the dewetting becomes more profound. It is also interesting to note that when ϵ_{CO}=0.0647kcal/mol, the system oscillates between the "dry" and "wet" states, indicating that $D = 6.8$Å is the critical distance for the graphite-like system with a ϵ_{CC}=0.027kcal/mol.

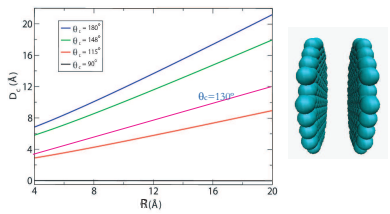

Figure 1. Schematic diagram for the two graphite-like plates system, and the dewetting critical distance versus the radius of the plates with different water contact angle (predicted from Eq. (1) of the macroscopic theory).

It is known from the macroscopic theory that the critical distance for drying between the plates will increase as the strength of the attractive interaction decreases[9]. In general, it can be shown that when the water contact angle with the plate, θ_c, is obtuse, the critical distance for dewetting $D_c \propto \cos\theta_c$.[9] The critical distance also increases linearly with the plate size when the plate is small.[9] Since the contact angle increases as the strength of the attraction between water and the plate decreases, the critical distance D_c should also increase. Here is the equation for the critical distance between two plates derived from a

simple model system[9]:

$$D_c = \frac{-2\gamma_{lv}\cos(\theta_c)}{(P - P_V) + b\frac{\gamma_{lv}}{R}} \quad (1)$$

where γ_{lv} is the liquid(water)-vapor surface tension, θ_c is the water contact angle on the surface, P is the external pressure and P_V vapor pressure, R is the radius of the plate, and b is a constant representing the geometrical factor (for cylindrical disks, b=2). The water contact angle for the graphite plate is only 86°,[13] so there is no dewetting transition for normal graphite plates (see Fig. 1). The water contact angle will increase when the carbon-water attraction is decreased, which might result in a dewetting transition, as shown in the above all-atom simulations. Similarly, the water contact angle for paraffin is estimated to be about 115°[12], which gives a critical distance of 6-8Å according to Eq. (1) (see Fig. 1), agreeing well with molecular dynamics simulations.[12] For the following fluorinated plates, a larger contact angle up to 130° was found[14], thus a dewetting transition with larger critical distance is expected. For even more hydrophobic model plates, such as those with a water contact angle of 148°, a critical distance up to 14Å has been found.[9]

2.2 Superhydrophobic Fluorocarbon Plates

Recently, Genzer and Efimenko have discovered a new family of molecules which display superhydrophobic surfaces in their mechanically assembled monolayers[14]. The common characteristic shared by these molecules is that they are all chain-like molecules with semi-fluorinated carbon groups. It has been previously found that fluorinated chains might possess a higher hydrophobicity than their hydrogenated counterparts. Thus from the above analysis based on the simple macroscopic theory (Eq. (1)), we might expect a stronger dewetting transition for these superhydrophobic fluorinated carbon monolayers (plates).

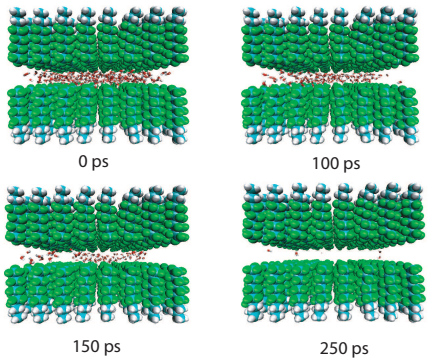

Figure 2. The snapshots of the double superhydrophobic fluorocarbon plates with D = 8Å. Only water molecules within the inter-plate gap region are shown. It takes only about 100-150ps for the sharp dewetting transition to finish once it initiates.

We devised a double plate system, with each plate consisting of 8×8 such molecules ($F(CF_2)_8(CH_2)_2SiH_3$) and their terminal -CF_3 groups facing each other (see Fig. 2). We

then solvate the double plate system in SPC water, with water molecules at least 8Å away from the solute surfaces. Figure 2 displays a few snapshots of the double plate system with separation distance D = 8Å. Only water molecules within the inter-plate gap region are shown for clarity. Clearly, a sharp dewetting transition is observed and the transition takes place within ∼100ps. More dewetting simulations reveal that a critical distance of D_c = 10Å exist for this system. These findings are also confirmed by rewetting simulations – starting from initial dry conditions and waiting for water molecules to rewet the region, indicating that the dry configurations are indeed thermodynamically more stable when the inter-plate distance D is less than 10Å. Another interesting point to notice is that although the time it takes to the initiation of the dewetting transition varies across different systems, the actual transition time after the initial diffusive motion is almost the same for all cases – about 100ps! This is also consistent with findings from the above graphite-like plates with reduced carbon-water interactions.

2.3 Melittin Tetramer

It is of great current interest to see whether any protein complex also displays a similar dewetting transition when the complex forms during the final stages of folding. A recent study by ten Wolde and Chandler on the collapse of a hydrophobic polymer using a coarse grained model shows that the mechanism of collapse is much like that of a first-order phase transition – the water drying and hydrophobic core formation happens roughly at the same time. The authors[15] thus speculate "Our findings would seem also pertinent to the mechanism of biological assembly, such as protein folding, but to demonstrate so with simulation will require an analogous simulation study of a protein-like chain." In this part of work, we study the water drying transition inside the a protein complex - the collapse of the melittin tetramer.

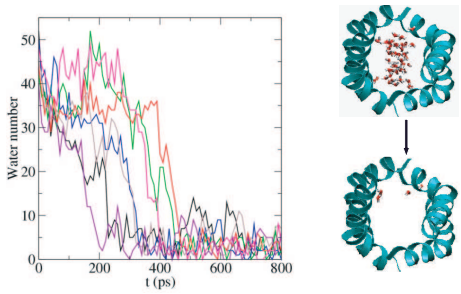

Figure 3. The number of water molecules inside the channel versus MD time and two representative snapshots of water molecules inside the channel of the melittin tetramer.

The two dimers of the melittin tetramer (initial crystal structure from PDB, 2mlt.pdb) were separated by a distance D to create a "nanoscale channel," then solvated in a water box with water molecules extending at least 8Å from the protein surface. Ten different initial configurations are prepared (same protein conformation in slightly different water boxes) for each distance D. Figure 3 shows the number of water molecules inside the channel versus the MD time for all trajectories with D=6.0 Å. All trajectories show that there

is a sharp dewetting transition and essentially all water molecules are expelled from the nanoscale channel after the transition. Figure 3 also shows two representative snapshots, one from before the transition, and one from after the transition. Again, the time it takes to the initiation of the dewetting transition varies with different initial configurations, but the actual transition time after the diffusive motion is almost the same for all trajectories – about 100ps! These results clearly indicate that there is a strong water drying (dewetting) transition inside this nanoscale melittin tetramer channel. Simulations with many other separation distances show that the drying transition critical distance D_c for this melittin tetramer system is approximately 5.5–7.0 Å, which is equivalent to 2-3 water molecule diameters. The reason why the melittin tetramer channel shows a drying transition while the previous two-domain protein BphC does not[16] appears to be two-fold. First, the melittin channel is like a tube while the inter-domain region in the two domain protein is a slab. It is less costly with respect to free energy to disrupt the hydrogen bonds in a tube-like channel. Second, the unique surface topology springing from the isoleucine residues in melittin disrupts the water hydrogen bonds in the channel thus destabilizes the wet state.

3 Conclusion

The nanoscale dewetting transitions provide a unique way to study the hydrophobic interaction in complex systems. In this mini-review, we have gone over some of our recent studies on the dewetting transition in the collapse of nanoscale graphite-like plates, fluorinated carbon monolayers, and protein melittin tetramer using molecular dynamics simulations. It was found that the normal graphite plates do not display any dewetting transition during the double plate collapse, while a reduction in carbon-water attraction can cause a dewetting transition, consistent with previous findings from carbon nanotubes by Hummer and coworkers.[11] The fluorinated carbon plates, on the other hand, display a strong dewetting transition with a critical distance up to 10Å and a very fast collapse speed ($\sim$100ps). In the melittin tetramer folding, we also observed an unexpected dewetting transition inside a nanoscale channel formed by the tetramer, with a channel size of up to 2-3 water diameters. These dewetting transitions, although occurring on a microscopic length scale, are reminiscent of the first order phase transition from liquid to vapor. The drying induced collapse provides an enormous driving force towards the further collapse. Finally, a simple macroscopic theory based on surface tensions can also provide useful guidelines for estimate of the dewetting critical distances from the water contact angle and plate size.

4 Simulation Methods

The GROMACS program is used for the molecular dynamics simulations of all the systems studied here. The OPLSAA force field is adopted for the fluorinated carbons and protein melittin tetramer (the graphite plate system is simple and the parameters are listed in the text above), and the SPC model for the explicit water solvent. The Particle Mesh Ewald (PME) method is used for the long-range electrostatic interactions, whereas a typical 10Å cutoff is applied to the van der Waals interactions. The timestep used for all molecular dynamics simulations is 1.0fs. A standard equilibration protocol is used, with a 1000 steps of conjugate gradient minimization, followed by a 100 ps position restrained

MD equilibration. The equilibrated systems are then used as the starting points for data collection (NPT, 1atm and 300K). In most of the "dewetting" simulations, the positions of the solute atoms are restrained in space with a harmonic potential (k = 10 kJ/mol/Å^2), unless otherwise explicitly stated.

Acknowledgments

I would like to thank Bruce Berne, Gerhard Hummer, Haiping Fang, Xin Li, Maria Eleftheriou, Xuhui Huang, Pu Liu, and Jingyuan Li for the help with the manuscript and many useful discussions.

References

1. C. Pangali, M. Rao, and B. J. Berne. Hydrophobic hydration around a pair of apolar species in water. *J. Chem. Phys.*, 71:2982–2990, 1979.
2. A. Wallqvist, E. Gallicchio, and R. M. Levy. A model for studying drying at hydrophobic interfaces: Structural and thermodynamic properties. *J. Phys. Chem. B*, 105:6745–6753, 2001.
3. M. E. Paulaitis and L. R. Pratt. Hydration theory for molecular biophysics. *Adv. Protein Chem.*, 62:283–310, 2002.
4. K. Lum and A. Luzar. Pathway to surface-induced phase transition of a confined fluid. *Phys. Rev. E.*, 56(6):6283–6286, 1997.
5. F. H. Stillinger. Structure in aqueous solutions of nonpolar solutes from the standpoint of scaled-particle theory. *J. Solution Chem.*, 2:141, 1973.
6. D. M. Huang and D. Chandler. The hydrophobic effect and the influence of solute-solvent attractions. *J. Phys. Chem. B*, 106:2047–2053, 2002.
7. K. Lum, D. Chandler, and J. D. Weeks. Hydrophobicity at small and large length scales. *J. Phys. Chem. B*, 103:4570–4577, 1999.
8. L. R. Pratt. Molecular theory of hydrophobic effects: She is too mean to have her name repeated. *Annu. Rev. Phys. Chem.*, 53:409–436, 2002.
9. X. Huang, C. J. Margulis, and B. J. Berne. The dewetting and collapse of nanoscale hydrophobic objects. *Proc. Nat. Acad. Sci. U.S.A.*, 100:11953–11958, 2003.
10. N. Choudhury and B. M. Pettitt. *J. Phys. Chem. B*, 109:6422–6429, 2005.
11. G. Hummer, J. R. Rasaiah, and J. P. Noworyta. Water conduction through the hydrophobic channel of a carbon nanotube. *Nature*, 414:188–190, 2001.
12. X. Huang, R. Zhou, and B. J. Berne. Drying and hydrophobic collapse of paraffin plates. *J. Phys. Chem. B*, 109:3546–3552, 2005.
13. M. Lundgren, N. L. Allen, and T. Cosgrove. Wetting of water and water/ethanol droplets on a non-polar surface: A molecular dynamics study. *Langmuir*, 18:10462–10466, 2002.
14. Jan Genzer and Kirill Efimenko. Creating long-lived superhydrophobic polymer surfaces through mechanically assembled monolayers. *Science*, 290:2130–2133, 2000.
15. P. R. T. Wolde and D. Chandler. Drying-induced hydrophobic polymer collapse. *Proc. Natl. Acad. Sci. U.S.A.*, 99:6539–6543, 2002.
16. R. Zhou, X. Huang, C. J. Margulius, and B. J. Berne. Hydrophobic collapse in multidomain protein folding. *Science*, 305:1605–1609, 2004.